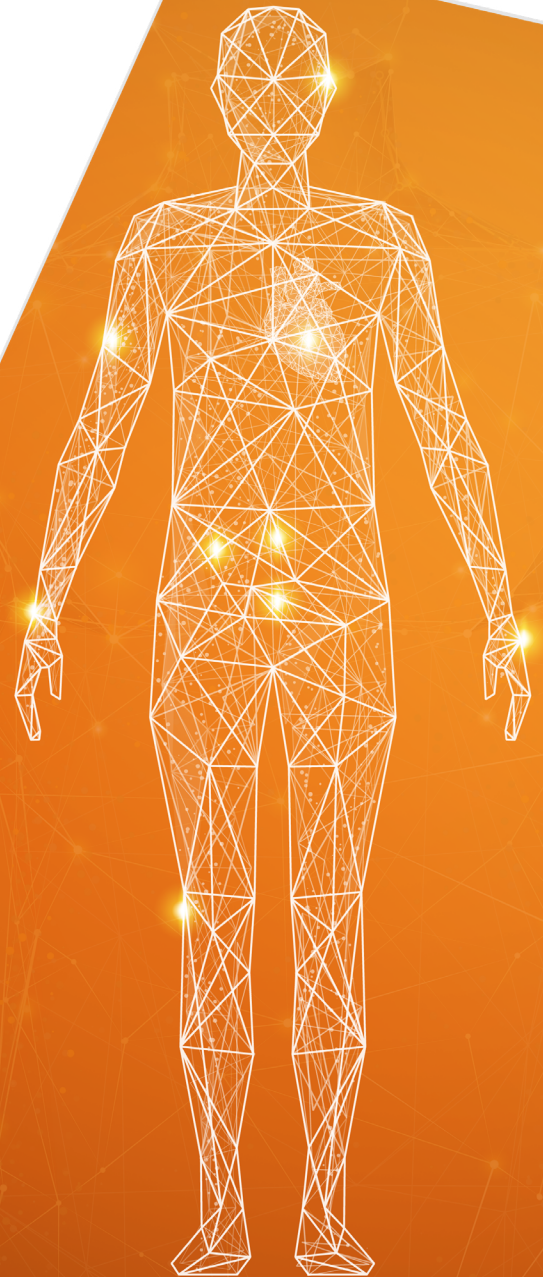


# Leveraging artificial intelligence to accelerate identification of **wtATTR-CM**

Overview of the wtATTR-CM Risk PredicTTR tool and the benefits of earlier diagnosis

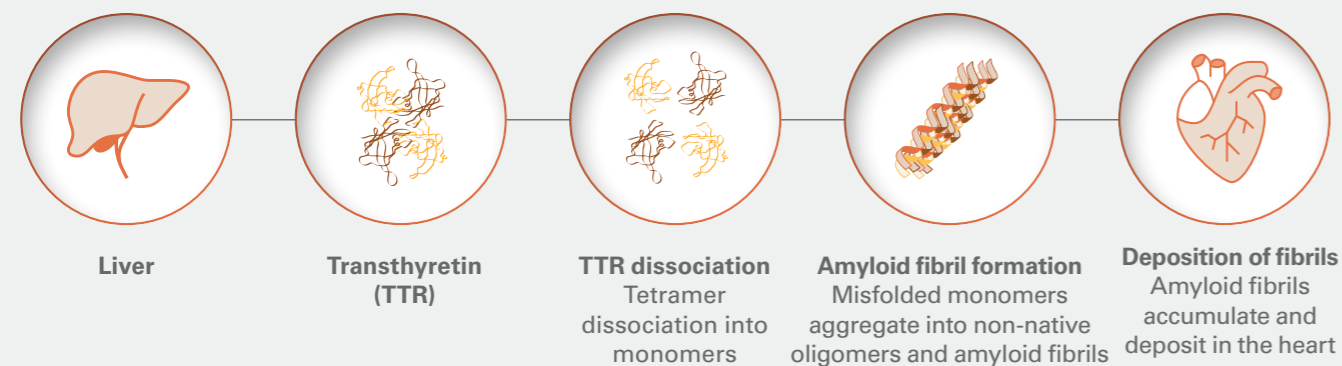


# ATTR-CM is an underdiagnosed, infiltrative disease often overlooked as a cause of heart failure.<sup>1</sup>

## What is ATTR-CM and what causes it?

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a systemic progressive disease associated with high levels of impairment, including in physical health and quality of life, and is ultimately fatal if left untreated<sup>2</sup>
- ATTR-CM results from the dissociation of transthyretin (TTR) proteins into monomers that misfold and aggregate, leading to TTR amyloid fibril formation and deposition in the myocardium, disrupting cardiac structure and function<sup>3</sup>

## Amyloidogenic TTR cascade<sup>1-3</sup>



ATTR-CM exists as two subtypes:

### Hereditary ATTR-CM (hATTR-CM)

Caused by a variation in the *TTR* gene<sup>4</sup>

### Wild-type ATTR-CM (wtATTR-CM)

Due to age-related misfolding of TTR<sup>4,5</sup>

## ATTR-CM is often misdiagnosed

- In a survey conducted by the Amyloidosis Research Consortium of patients with ATTR-CM, 17% of all respondents reported visiting five different physicians before receiving the correct diagnosis<sup>6</sup>
- Once diagnosed, untreated patients have a median survival of approximately 2–5 years, depending on subtype and mutation<sup>5,7,8</sup>

▶ **Given the underdiagnosis, misdiagnosis, and high morbidity of untreated ATTR-CM, improved screening to enhance earlier diagnosis is essential to expedite treatment of these patients**

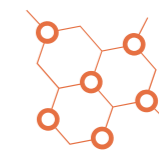
# Leveraging a machine-learning model to support identification of ATTR-CM: *The wtATTR-CM Risk PredictTTR*

## What is machine learning?

- Machine learning is an application of artificial intelligence (AI) that uses data and algorithms to learn from prior experience to make more accurate predictions.<sup>9,10</sup> It has been successfully used in medicine, from drug discovery to recognition of disease<sup>11</sup>
- Supervised machine learning is a subset of machine learning where the model is trained to use labelled datasets to predict or classify an outcome of interest.<sup>12,13</sup> As input data is fed into the model, it adjusts its weights until the model has been fitted appropriately.<sup>10,14</sup> The model is then used to make predictions on new data<sup>10,14</sup>
- An example of machine learning used in medicine today is the automated interpretation of the EKG, where pattern recognition is performed to select from a limited set of diagnoses.<sup>14</sup> The computer is approximating what a trained physician is already capable of doing with high accuracy<sup>14</sup>



Pattern recognition on medical images for faster diagnoses and to evaluate disease progression



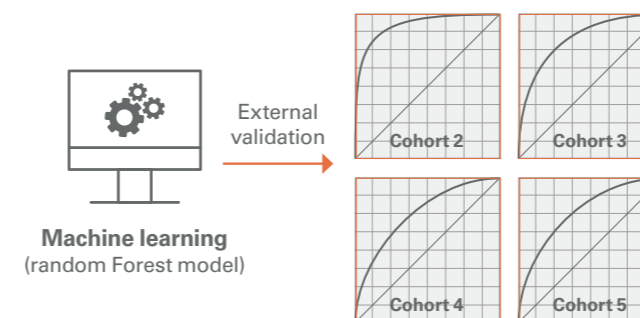
Predicting pharmaceutical properties of molecular compounds and targets for drug discovery



Developing techniques to detect new predictive models for recognizing diseases

## What is the wtATTR-CM Risk PredictTTR and what does it do?

- The wtATTR-CM Risk PredictTTR is a web-based machine-learning tool developed to help physicians identify people who are potentially at risk of wtATTR-CM in a given heart-failure population.<sup>15</sup> It leverages an AI-derived algorithm to analyse patient-level diagnostic data and to determine the likelihood of wtATTR-CM in individual patients<sup>15</sup>



- The wtATTR-CM Risk PredictTTR was initially derived and tested in a case-controlled cohort of over 2,000 US patients, extracted from an IQVIA database of over 300 million US patients.<sup>15</sup> It was then validated in three nationally representative cohorts in the US, representing approximately 88 million US patients in total<sup>15</sup>

- It was further tested in an external single-centre electronic-health-record-based cohort of almost 40,000 US patients.<sup>15</sup> By recognising several cardiac and non-cardiac clinical features associated with wtATTR-CM, the machine-learning model successfully identified patients with cardiac amyloidosis in the derivation cohort and all four validation cohorts, providing a systematic framework to increase the suspicion of ATTR-CM in patients with heart failure<sup>15</sup>

## Use of the wtATTR-CM Risk PredictTTR in clinical practice could lead to earlier targeted testing and identification of wtATTR-CM in at-risk patients, potentially leading to earlier treatment<sup>15</sup>

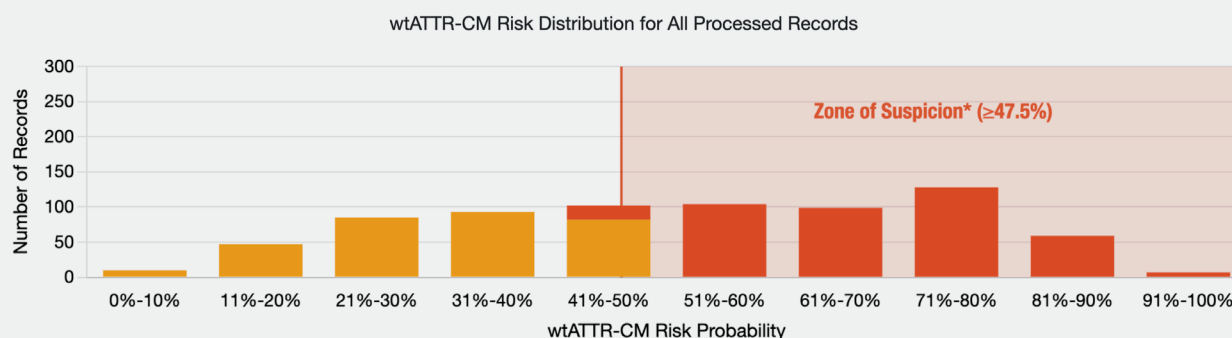
- The wtATTR-CM Risk PredictTTR can calculate the probability of wtATTR-CM in patients with heart failure, predicting wtATTR-CM versus non-amyloid heart failure with up to 87% accuracy, 87% specificity, and 87% sensitivity<sup>15</sup>
- Up to 50,000 de-identified patient records can be uploaded into the wtATTR-CM Risk PredictTTR, which analyses the data and generates a probability score.<sup>15</sup> These scores are then downloaded and used to re-identify individuals who should be considered for further evaluation, including further confirmatory testing for wtATTR-CM<sup>15</sup>
- The use of de-identified data ensures data privacy is maintained. In addition, the algorithm leveraged by the tool does not learn from the data supplied by the user, further securing data privacy

## YOUR RISK predicTTR RESULTS

### 1 Results Explained

The Risk predicTTR:

- Was able to process 734 out of 734 records you have submitted
- Found 417 records within the Zone of Suspicion (risk probability  $\geq 47.5\%$ )\*, for which we recommend pursuing additional follow-up action
- 0 records had codes that were not utilised. Please see the report for codes that were not utilised or identified by the system



\*The optimal Zone of Suspicion Risk Probability Threshold was determined to be 47.5%, as it maximised the performance of the Random Forest model in testing.<sup>1</sup>

## Improving the clinical recognition and time-to-diagnosis of wtATTR-CM can enable earlier treatment initiation and improve patient outcomes<sup>13</sup>



To learn more about and/or to schedule a demo of the wtATTR-CM Risk PredictTTR tool, please go to [insert webpage link(s) information and/or QR code(s) here] or contact your local Pfizer representative [insert contact information here]



**References:** 1. Witteles RM, et al. *JACC Heart Fail* 2019;7(8):709–16. 2. Stewart M, et al. *Neurol Ther* 2018;7:349–64. 3. Nativi-Nicolau J, Maurer MS. *Curr Opin Cardiol* 2018;33(5):571–9. 4. Sipe JD, et al. *Amyloid* 2016;23:209–13. 5. Connors LH, et al. *Circulation* 2016;133:282–90. 6. Adams D, et al. *Orphanet J Rare Dis* 2017;12(Suppl 1):165. 7. Maurer MS, et al. *Circulation* 2017;135:1357–77. 8. Grogan M, et al. *J Am Coll Cardiol* 2016;68(10):1014–20. 9. Olsen CR, et al. *Am Heart J* 2020;229:1–17. 10. Schaefer et al. *Orphanet J Rare Dis* 2020;15:145. 11. Shah P, et al. *NPJ Digit Med* 2019;2:69. 12. Gupta R, et al. *Mol Divers* 2021;25(3):1315–1360. 13. Jiang T, et al. *Behav Ther* 2020;51(5):675–687. 14. Deo RC. *Circulation* 2015 17;132(20):1920–30. 15. Huda A, et al. *Nat Commun* 2021;12:2725.